Statistical Review and Evaluation

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NDA#: 21-213/Class 6-S

Applicant: Merck Research Laboratories

Name of Drug: Mevacor (lovastatin 10 mg for OTC use)

Documents Reviewed: Volume 1 dated December 10, 1999, submission dated March 2, 2000, and submission dated March 13, 2000

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Note: All tables and figures except Figure 4 are taken from the sponsor's submission

Background

The sponsor has submitted several bodies of data in support of an application to change Mevacor's 10 mg status from a prescription to an over-the-counter dose. The definition of the 'OTC population' is *"men at least 40 years of age and postmenopausal women (at least 1 year past menses) with out a history of CHD., diabetes stroke, or high blood pressure, and with total cholesterol levels of 200 to 240 mg/dL and low density lipoprotein-cholesterol (LDL-C) levels of at least 130 mg/dL"*. The submission includes data from epidemiologic (observational) studies (Atherosclerosis Risk in Communities [ARIC] and the Framingham Heart Study), controlled clinical trials (075 and AFCAPS), and 'consumer use' studies (076, 077, 079).

Trial 075 enrolled patients with total-C between 200 and 240 and LDL-C between 130 and 160 after diet and used a dose of 10 mg/day or placebo. AFCAPS enrolled a total of 6605 patients who were "generally healthy middle-aged and older men and women without CHD and with average TC and LDL-C, and with below average HDL-C" and used 20 mg/day to statrt with possible titration to 40 mg/day. Of these 6605 subjects, 3805 met the 'OTC eligible' definition.

Trials 076 and 077 were open label studies evaluating compliance and persistence of use in patients who self-selected to receive 10 mg lovastatin with total cholesterol (total-C) between 200 and 240. Trial 079 also evaluated compliance and persistence and enrolled patients with total-C at most 240 and LDL at least 130. For purposes of this review, trials 076 and 079 are useful for the information of LDL-C lowering and compliance rates. A review of their central purpose and data can be found elsewhere.

The sponsor has used the observational data for two purposes: 1) to estimate, where possible, the risk of CHD events in the 'OTC population' and 2) estimate the potential population benefit available to those who take 10 mg lovastatin/day. For example: "By modeling of epidemiological data, it is estimated that the risk of a CHD event can be reduced by approximately 1% over 5 years, 2% over 10 years, and 4 to 5% over 20 years *given the assumptions used in the analysis*" [italics added]. This review does not examine conclusions about the potential benefit of lovastatin based on observational data primarily because 1) the analyses do not include

information about compliance and the effect of non-compliance on the CHD risk in an individual, 2) the data describes observed levels of cholesterol rather than the effect of intervention which lowers cholesterol levels, and 3) the effect of various assumptions is not evident. In fact, 1) and 3) are common to the prospective, controlled data. Beneath the density of data and analyses supplied by the sponsor is the lurking problem that there is no way to produce a *reliable* estimation of benefit, precisely because of numerous assumptions required to make *any* estimate.

Lipid Lowering

There is the further question of whether a reliable estimate of benefit is necessary. Is demonstration of LDL-C lowering in this population sufficient by itself for OTC use of lovastatin simply because it can be argued that there will be *some, but largely unknown* benefit? If the answer is 'yes' then trials 075 (placebo-controlled trial using 10 mg for 12 weeks) and the 076 (24 weeks) and 079 (8 weeks) provide sample distributions of LDL-C lowering in patients who take 10 mg lovastatin. In addition, the AFCAPS trial (5 years) provides a sample distribution of LDL-C lowering in patients who started on 20 mg and had the opportunity to be titrated to 40 mg. **Table 1** displays the mean lipid lowering results of these 4 studies. **Figure 1** displays the cumulative distribution curves for 075, 076 (at two time points) and 079. These curves are based upon observed data and not last observation carried forward. **Figure 2** displays the cumulative distribution curves for *baseline values* in data bases, including NHANES III. **(See Dr. Parks' review for a thorough discussion of these results.)** Since these curves come from different studies, comparing them with statistical methods is not appropriate. However, despite dropouts, different time points of evaluation, and differences in design, it appears that there is considerable overlap between the distributions of LDL-C lowering provided by studies which administered 10 mg lovastatin and AFCAPS which started with 20 mg and titrated to 40 mg in 51.5% of the OTC eligible sample. Interestingly, LDL-C lowering at 1 year was no different among those who were not titrated to 40 mg compared to those who were (-25.3% vs -23.4%, respectively). *As of now, there is no criterion or standard that the distribution of LDL-C lowering on 10 mg must meet relative to that in the AFCAPS trial. One can only say that an unknown proportion of patients who take 10 mg continually would presumably get the same putative benefit had they been on 20-40 mg.*

Ultimately, the sponsor's case rests on the following transitional logic: Since the '10 mg' trials 075, 076 and 079 produced LDL-C lowering comparable to AFCAPS (20-40 mg) and AFCAPS suggests a CHD reduction relative to placebo after 5 years in a subset of patients defined as 'OTC eligible', then the general OTC population will gain a benefit in CHD outcomes. **Table 2** displays the event rates in AFCAPS and **Figure 3** displays the Kaplan-Meier curves of the treatment groups. Note that the sponsor claims that the difference in event rates translates into treating 43=1/(.053-.030) patients for 5 years to prevent 1 cardiac primary endpoint. The primary CHD endpoints for this purpose are *fatal or non-fatal MI, unstable angina, or sudden cardiac death.* Thus, if a relative incidence of CHD outcomes is required as explicit evidence of benefit, then we must look to the best data available to estimate that benefit,

and the AFCAPS trial is the only adequate and well-controlled trial which used lovastatin as an intervention and recorded the incidence of CHD.

What is Missing from AFCAPS?

Because compliance in taking medication was high and the doses were all greater than 10 mg in this controlled trial, the AFCAPS subset analysis presents an upper bound of clinical benefit for some population of which this sample is supposedly representative.

There are two critical factors that must be taken into account: 1) the compliance in AFCAPS is probably much greater than that in a true OTC setting and 2) once a patient stops taking medication, the risk of a future event is unknown, although we could presume that it is greater than if the patient had stayed on medication. There is no data in the submission that is useful in estimating compliance rates over 5-years or future risk as a function of prior exposure to drug. It is precisely the information about compliance and the change in hazard of a CHD event after dropping medication which are not available in AFCAPS or any body of data submitted by the sponsor, with the notable exception that the proportion of patients who dropped medication in two consumer use studies (6-months and 8-weeks) was approximately 30%, hardly an encouraging figure for as little as a 5-year benefit.

Using AFCAPS to Project Event Incidence

In order to demonstrate the issues involved in accurately projecting realistic estimates of a 5-year benefit on drug using the lovastatin and placebo groups in AFCAPS, and taking previous considerations into account, consider the following highly simplified scheme:

I) We hypothetically record only that someone has stopped medication before or after 2.5 years, the midpoint of the trial duration. Thus there are two independent cohorts, one that drops before 2.5 years (cohort A) and one that drops after 2.5 years (cohort B).

II) We assign a discrete hazard to the 2 time periods for patients who are taking drug:

1) the hazard of an event *before* 2.5 years in cohort A (H_{A1})
2) the hazard of an event *after* 2.5 years in cohort A (H_{A2})
3) the hazard of an event *before* 2.5 years in cohort B (H_{B1})
4) the hazard of an event *after* 2.5 years in cohort B (H_{B2})

III) We estimate these hazards by using a linear combination (weighted average) of discrete hazards estimated from the drug and placebo groups in AFCAPS. This represents a 'best case scenario' for the drug group since these patients were highly compliant and were taking 20-40 mg rather than 10 mg lovastatin. *Assigning weights is meant to make up for the fact that we do not know the relationship between the CHD event probability and how long one stays on medication, but maybe using an average of what we* ***can*** *estimate will be useful.*

For cohort B, the probability of having an event before 5 years is

$f_B=1 - (1 - H_{B1})*(1 - H_{B2})$

Finally, we must assign proportions of the population who will be in cohorts A and B. These will be "cA" and 'cB", respectively. *Assigning values to cA and cB is meant to make up for the fact that we do not have knowledge of the distribution of medication dropouts.*

As a last refinement, suppose that we assume that there are patients who will drop medication so soon after starting that they get no benefit at all and so their probability of an event within 5 years is simply the placebo probability in AFCAPS, .056. Conversely, there will be some patients who get full benefit because they would have stayed on drug for 5 years if not for an event. Then their probability of an event is the drug probability in AFCAPs, .032. Finally, we assign c0, cA, cB and c5 as the percentages of the entire cohort who fall into the now 4 subcohorts. Using the results of the consumer studies, we assign c0=.3. We then choose cA=.2, .3, or .4, cB =.1 or .2, and c5=1- (c0 + cA + cB). The weights w1, w2, and w3 were each taken to be 0, .2, .4, .6, .8, or 1.0.

Thus the total percentage of patients who are projected to have an event before 5 years is

$P=.056*c0 +cA*f_A + cB*f_B + .032* c5$

As anticipated, the freedom of variation in the compliance rate and weights used to estimate the risk in cohorts A and B produced values over a wide range of projected event incidences from 3.2% on lovastatin to 5.6% on placebo, the Kaplan-Meier estimates of event rates using the simplified discrete hazards from the trial itself, i.e. using p1-p4.

Figure 4 displays the cumulative frequency curves for the 6 usable combinations of c0-c3 (recall that the numbers P on the horizontal axis are simply computed values, not values of a random variable). The relative positions of the curves are consistent with the notion that the lower the chance of dropping medication in the first 2.5 years, the tendency is to have lower event rates.

Discussion and Conclusion

In this application there is no hypothesis other than the *plausibility* that some OTC eligible patients will get at least a *de minimus* risk reduction in CHD in a realistic (not controlled) setting. The only controlled data comes from a subset of the AFCAPS trial, so that one must regard this subset analysis in one trial to be the substantiation that lovastatin does indeed reduce the risk of CHD events in the 'OTC eligible' population. Reliable estimates of risk reduction in the population do not reside in observational data or controlled data without the availabilty of data on varying exposure to drug over a meaningful period of time due to lack of compliance, and the changing CHD event hazard resulting from a curtailed exposure of 10 mg/day. This consideration is especially important if a good estimate of a benefit-to-risk ratio is needed. At present, access to such as estimate requires a randomized, controlled clinical trial.

IV) From AFCAPS we estimate that the discrete hazards of an event after 2.5 and 5 years to be:

1) p1= 2.65% in the **placebo** group at **2.5 years**: 95% confidence interval (1.9%, 3.4%). In this case, the denominator is the total number of people in the placebo group (1921) and the numerator is the number of patients who have an event *within* 2.5 years (51).

2) p2= 1.91% in the **lovastatin** group at **2.5 years**: 95% confidence interval (1.3%,2 .5%). In this case, the denominator is the total number of people in the lovastatin group (1884) and the numerator is the number of patients who have an event *within* 2.5 years (36).

3) p3=3.05% in the **placebo** group at **5 years:** 95% confidence interval (2.2%, 3.8%)
In this case, the denominator is the number of people in the placebo group who were still at risk at 2.5 years (1870) and the numerator is the number of patients who have an event in the *following* 2.5 years (57)

4) p4=1.30% in the **lovastatin** group at **5 years:** 95% confidence interval (0.8%, 1.8%)
In this case, the denominator is the number of people in the lovastatin group who were still at risk at 2.5 years (1848) and the numerator is the number of patients who have an event in the *following* 2.5 years (24)

Dropouts due to reasons other than a CHD event are ignored.

We then form expressions for the 'H's':

H_{A1}=w1*p2 + (1-w1)*p1
H_{A2}=w2*H_{A1} + (1-w2)*p3
H_{B1} =p2
H_{B2}= w3*p2 + (1-w3)*[p2 +(p3+p4)/2]/2

H_{A1} is taken to be a weighted average of event experience on drug and placebo during the first 2.5 years.

H_{A2} is taken to be a weighted average of the experience in the first 2.5 years and placebo experience in the second 2.5 years.

H_{B1} is taken to be simply the experience of the drug group in the first 2.5 years

H_{B2} is taken to be a weighted average of experience of the drug group in the first 2.5 years and the simple average of experience of the drug and placebo groups in both epochs

For cohort A, the probability of having an event before 5 years is

f_A=1 - (1 - H_{A1})*(1 - H_{A2})

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cc:
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HFD-510/MParks, MSimoneau
HFD-715/DHoberman, TSahlroot, DOB2, Chron

Table 1

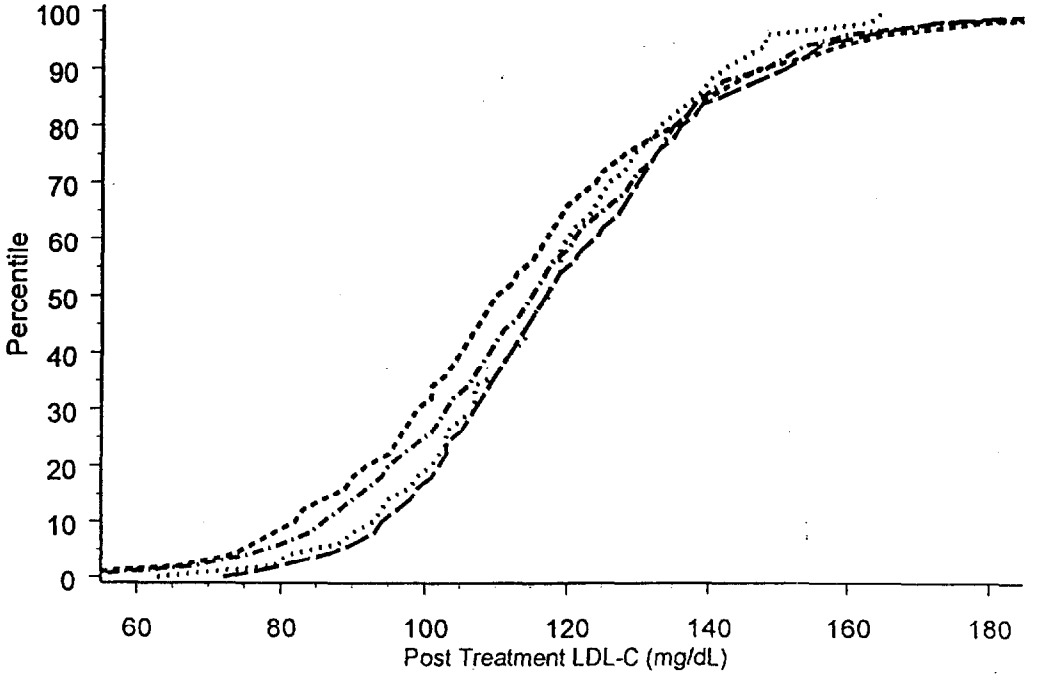
Lipid-lowering Efficacy of Lovastatin in Protocols 075, 076, 079, and in the Nonprescription Lovastatin Treatment-Eligible AFCAPS/TexCAPS Subset

	Mean Change (%) from Baseline							
	LDL-C		Total-C		HDL-C		Total-C/HDL-C	
	N	%	N	%	n	%	n	%
Protocol 075 (Efficacy Study)								
Week 6	95	-19.3	96	-12.6	96	5.7	96	-16.8
Week 12	96	-17.5	97	-11.4	97	6.7	97	-16.4
Protocol 076 (Pharmacy Study)								
Week 8†	568	-21.7	571	-12.9	571	6.9	571	-15.4
Week 24†	494	-23.9	500	-15.7	499	6.0	499	-17.8
Protocol 079 (Restricted Access Study)								
Week 8†	288	-18.4	293	-10.4	293	5.4	293	-12.9
AFCAPS/TexCAPS Nonprescription treatment-eligible								
1 Year	3805	-25.3	3805	-18.6	3805	5.6	3805	-21.7

† Includes only patients with complete data at baseline and follow-up visit.

Figure 1

LDL-Cholesterol
Cumulative Distribution Function



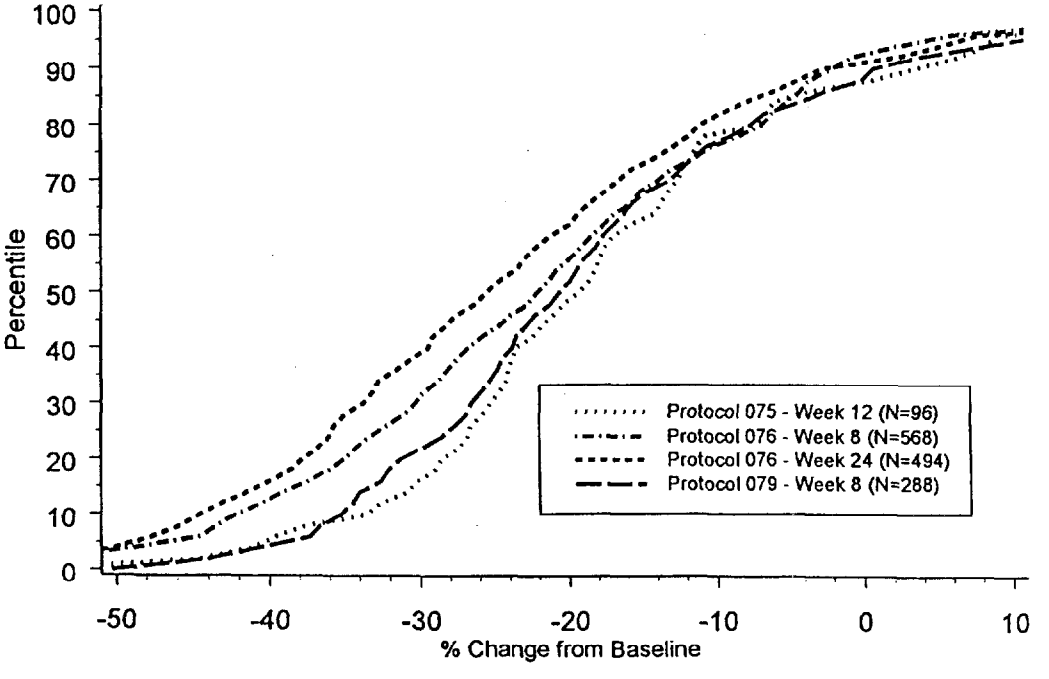


Figure 2

Baseline LDL-Cholesterol (mg/dL)
Cumulative Distribution Function by Gender

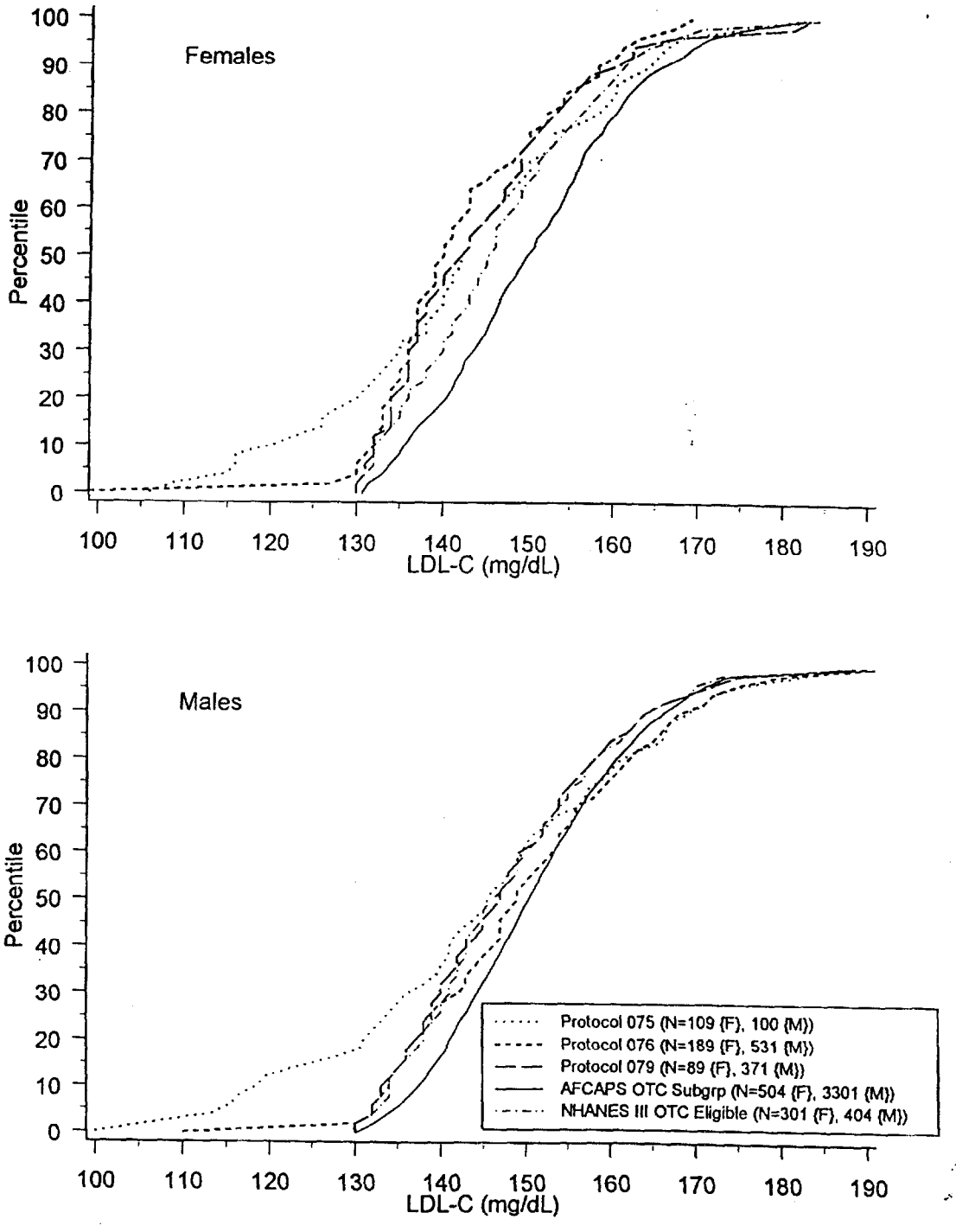


Table 2

Primary Endpoint† Event Rate Risk Reduction in AFCAPS/TexCAPS, by Nonprescription Lovastatin Treatment Eligibility

Nonprescription lovastatin eligibility	Events/ Patients (%)		5-Year K-M‡ Event Rate (%)		NNT§	Events avoided/ 10,000 treated‖	Risk Reduction (95% CI)	p-Value
	Placebo	Lovastatin	Placebo	Lovastatin				
Eligible	108/1921 (5.6)	60/1884 (3.2)	5.3	3.0	43	233	0.440 (0.233; 0.592)	.001
Not eligible	75/1380 (5.4)	56/1420 (3.9)	5.0	3.6	71	141	0.277 (-0.023; 0.049)	.067
Combined	183/3301 (5.5)	116/3304 (3.5)	5.2	3.3	54	185	0.373 (0.209; 0.503)	.001

† Nonfatal MI, Unstable Angina, Fatal CHD.

‡ Estimated by Kaplan-Meier survival method.

§ Number of persons needed to treat for the indicated time period to avoid one event = [(1/difference between placebo and lovastatin) x 100].

‖ Number of events avoided per 10,000 patients treated for the indicated time period = (10,000/NNT).

Figure 3

Primary Endpoint Event-Free Survival Curves Among AFCAPS/TexCAPS Patients Eligible for Nonprescription Lovastatin, by Treatment

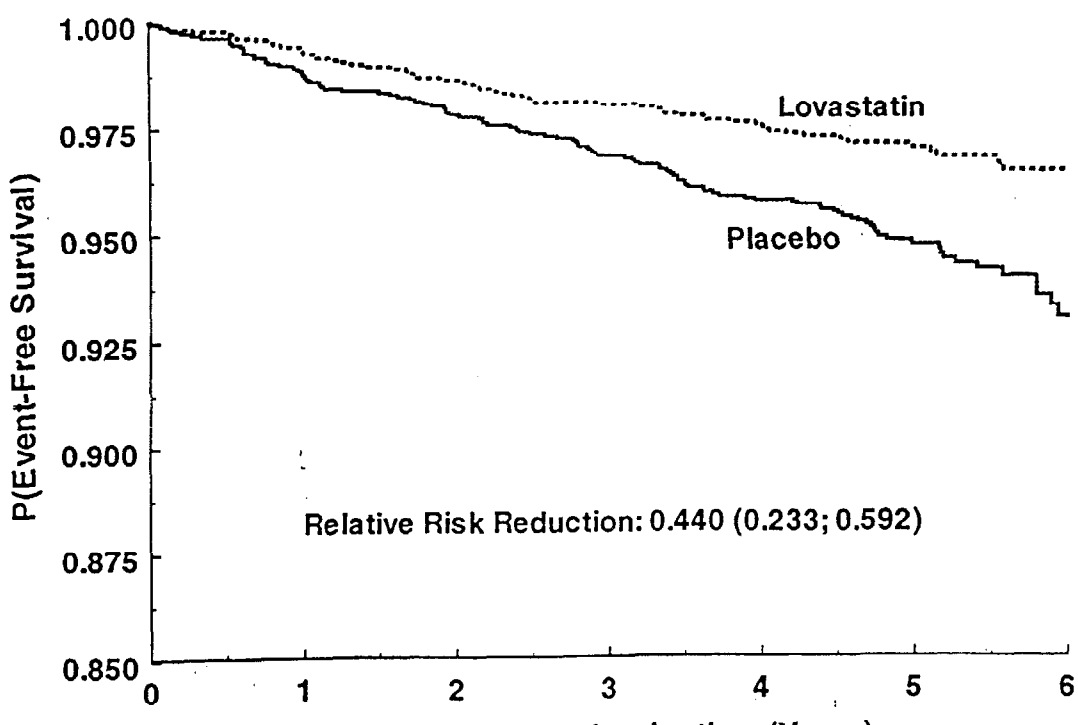
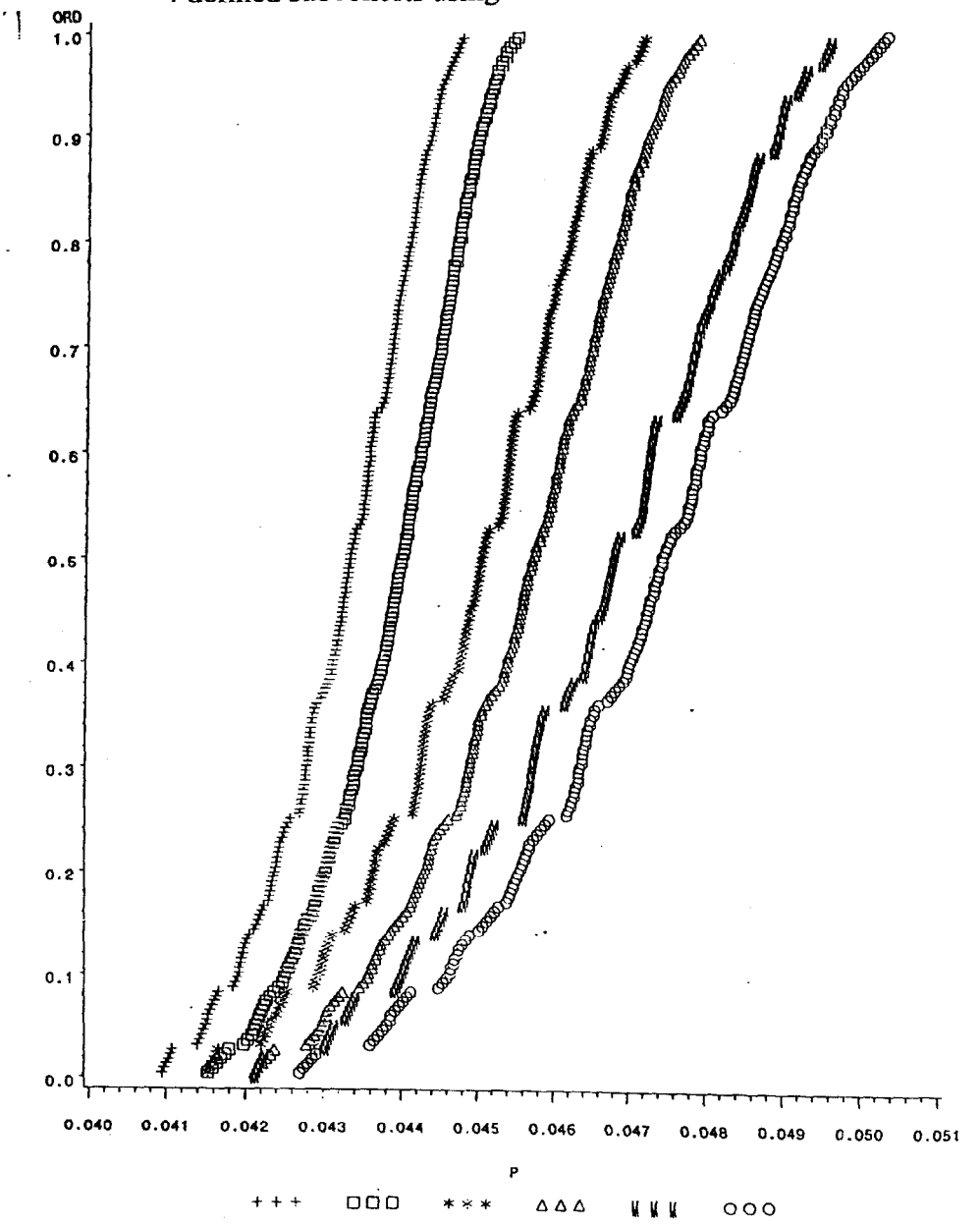


Figure 4

Cumulative frequency of projected event incidence given six scenarios of non-compliance in the 4 defined subcohorts using results in AFCAPS



The different symbols correspond to different vectors of dropout percentages for each of the 4 cohorts, i,e, different values of c0, cA, cB, and c5, respectively, where

+++= {.3, .2, .1, .4}
□□□ = {.3, .2, .2, .3}
***= {.3, .3, .1, .3}
ΔΔΔ = {.3, .3, .2, .2}
MMM={.3, .4, .1, .2}
ooo= {.3, .4, .2, .1}